UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,064	11/05/2003	H. William Bosch	029318-0978	6295

31049 7590 07/23/2007

ELAN DRUG DELIVERY, INC.
C/O FOLEY & LARDNER LLP
3000 K STREET, N.W.
SUITE 500
WASHINGTON, DC 20007-5109

EXAMINER	
TRAN, SUSAN T	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
07/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/701,064	**Applicant(s)** BOSCH ET AL.	
	Examiner Susan T. Tran	**Art Unit** 1615	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 July 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *16*.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-24,36-75 and 87-90*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see Detailed Action.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

SUSAN TRAN
PRIMARY EXAMINER

Art Unit: 1615

DETAILED ACTION

Applicant argues that Kuczynski does not remedy the deficiencies of Liversidge. Kuczynski, like Liversidge, fails to teach or suggest nanoparticulate glipizide compositions. Instead, Kuczynski provides the general teachings that glipizide is an oral blood-glucose lowering drug indicated for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus, and discloses a composition comprising *granules of 2 to 50 mg of glipizide*. Thus, Kuczynski fails to disclose a composition comprising nanoparticles of glipizide.

Applicant argues that Liversidge discloses nanoparticles of danazol, a *steroid* drug. Liversidge merely provides a laundry list of drug substances selected from known classes of drugs, including antidiabetic agents, that may be *suitable* for the invention. Liversidge does not specifically teach, however, forming a nanoparticulate composition comprising glipizide. Thus, the Office Action's characterization of Liversidge is factually inaccurate.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further, Liversidge is relied upon for the teachings with the four-wall patent. Liversidge cannot be limited to the best mode invention as described in the examples. A reference may be relied upon for all that it would have reasonably suggested to one

having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.).

Liversidge teaches the claimed nanoparticles having the claimed particle size distribution, as well the claimed surfactant in the claimed amount. Liversidge also teaches the active agent suitable for the preparation of the nanoparticles includes anti-diabetic agent (column 3, lines 57-58). The only deficient by Liversidge is the claimed anti-diabetic agent such as glipizide. Kuczynsky is cited for the teaching of glipizide is a known anti-diabetic agent in pharmaceutical art. Accordingly, it would have been obvious to one of ordinary skill in the art to modify the nanoparticles of Liversidge using glipizide as an anti-diabetic agent, because Kuczynski teaches glipizide is a well known anti-diabetic agent, and because Kuczynski teaches glipizide is odorless and advantage antidiabetic agent useful for the treatment of diabetes.

Applicant argues that the Office Action, in its allegation of obviousness, presumes some motivation for wanting to specifically prepare nanoparticulate compositions containing glipizide in preference to other anti-diabetic agents, despite the lack of reasonable evidence for such motivation. The Office Action's presumption relies, at best, on the "obvious to try" standard. As *KSR Int'l Co. v. Teleflex Inc.* states, "w]hen there is a design need or market pressure to solve a problem and *there are a finite number of identified, predictable solutions,* a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." This standard, however, may not be applied in the present application because there are an infinite number of

known anti-diabetic agents available on the market, such that there are too many possible anti-diabetic agents to render the particular claimed glipizide nanoparticles obvious.

To clarify the record, the office action did not cite "*KSR*" case to support the 103(a) rejection of record.

Applicant argues that the Office Action, at page 9, alleges that Liversidge recognizes the need in pharmaceutical arts to obtain formulations having high bioavailability. The Office Action, however, does not consider that Liversidge also teaches that *"not every combination of surface modifier and drug substance provides the desired results." See id.* at col. 7, lines 21-23. Further, Liversidge provides unsuccessful examples (Examples A-F) that confirm that selection of surface modifiers and drug substances is not a trivial endeavor and that some combinations fail to result in suitable compositions. Moreover, the Office Action seems to presume that any nanoparticulate formulation of a drug will improve the bioavailability of the drug. However, such presumption finds no support in the cited prior art or in the knowledge regarding the different nature of drugs and drug formulations. Accordingly, not only, as stated by Liversidge, not all drugs may be formulated into nanoparticulate compositions, but also, as demonstrated above, not all drugs may have their pharmacokinetic properties improved by nanoparticulate formulations. Thus, the Office Action's allegation is impermissible.

However, applicant's arguments are not persuasive for the following reasons: 1) the list of possible surface recited in the present claims are huge, it includes most of the

possible surface modifiers (see for example claim 11); 2) the independent claims do not require any specific surface active agent; and 3) examples 7-14 of Liversidge show the use of different surface modifiers can result in the same properties desired. Thus, it would have been obvious to one of ordinary skill in the art to prepare the claimed invention given the teachings of Liversidge in view of Kuczynsky, because Liversidge teaches the claimed nanoparticle with the claimed particle size distribution in combination with the claimed surfactant in the claimed amount to obtain a formulation having high bioavailability (abstract), and because Kuczynsky teaches glipizide is a well known anti-diabetic agent.

Further, Liversidge teaches that many factors can affect bioavailability of a drug including the dosage form and various properties, e.g., dissolution rate of the drug. Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water. Poorly water soluble drugs, i.e., those having a solubility less than about 10 mg/ml, tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. Moreover, poorly water soluble drugs tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with fully soluble drug substances. Kuczynsky teaches that glipizide is known in the art to be insoluble both in water and alcohol. Thus, to improve bioavailability of this drug, the skilled artisan would have been motivated to modify glipizide compound in view of the teaching of Liversidge, because Liversidge suggests how to improve bioavailability of water-insoluble drugs including anti-diabetic agent.

Accordingly, the 103(a) rejection over Liversidge in view of Kuczynsky is maintained.

Applicant argues that the inability of Liversidge and Kuczynski to teach or suggest the invention of claims 1-8, 10-11, 13-15, 17-35, 40-43, 45-50, 52-53, 55-65, 67-68 and 70-90 is demonstrated above. The additional reference, Parikh, does not remedy the deficiencies of Liversidge and Kuczynski. Rather, the disclosure of Parikh is directed to compositions comprising microparticles of water-insoluble drugs and methods of producing these compositions. Parikh fails to teach or disclose nanoparticulate glipizide compositions. Thus, Parikh fails to remedy the deficiencies of Liversidge and Kuczynski.

In response to applicant's argument, Parikh is cited in combination with Liversidge and Kuczynski. Parikh is relied upon for teaching of using mixture of surface modifiers. Nanoparticulate glipizide is taught in Liversidge in view of Kuczynski.

SUSAN TRAN
PRIMARY EXAMINER
AU 1615